REMARKS

Upon entry of the foregoing amendment, claims 1, 44, 46-52, and 55-65 are pending in the application, with 1, 57-59, 61, and 63-65 being the independent claims. Claim 45 has been canceled without prejudice or disclaimer. Claims 1, 44, 57-59, 61, and 63-65 have been amended. Support for the phrase "dosage form is found in the specification at page 6, line 26 to page 7, line 5. Support for the recitation that the enhancer is the only enhancer present in the dosage form is found in the examples, all of which utilize a single enhancer in the dosage form. The specification further states that the term "enhancer encompasses a combination of one or more enhancers (page 9, lines 22-24). Thus, the specification clearly contemplates formulations and dosage forms containing only a single enhancer. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections Under 35 U.S.C. § 103

(A) Claims 1, 44-51, 55, and 56 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Teng *et al.* (International Publication No. W0 99/01579). (Office Action, page 2). Applicants respectfully traverse this rejection.

The Examiner acknowledges that Teng *et al.* teaches the use of a C10 enhancer at a higher concentration than is presently claimed but does not consider this to be a teaching away from using a lower concentration. (Office Action, page 10). The Examiner further states that "one of ordinary skill in the art would expect that the use of any amount of enhancer would still result in effective delivery." (Office Action, page 10).

Applicants respectfully disagree. Claim 45 has been canceled, rendering that portion of the rejection moot. The present claims as amended are directed to a method for enhancing the intracellular delivery of a nucleic acid-based drug in a mammal comprising administering to the mammal a dosage form comprising the nucleic acid-based drug and a single enhancer which is a C10 fatty acid or a salt thereof and is the only enhancer present in the dosage form. The present specification discloses that a C10 fatty acid salt at very low concentrations (0.01 to 13 mM) is sufficient to enhance the intracellular delivery of a nucleic acid in the absence of

any other enhancers. The present specification further demonstrates (*e.g.*, in Example 1) that C10 at higher levels is quite toxic to cultured cells, indicating the need to use lower amounts of enhancer. Yet, the specification demonstrates that the claimed low concentration range is sufficient to achieve a substantial enhancement of intracellular delivery with minimal toxicity.

In contrast, Teng *et al.* discloses only a single formulation (Formulation 2) containing a C10 fatty acid (1% caprate (51.5 mM)) as the only enhancer (page 46). While use of Formulation 2 provided 5% absorption of an oligonucleotide, Formulation 3 combining 0.5% caprate and 0.5% laurate was three times as effective (page 48, lines 16-25). Teng *et al.* further shows that increasingly complicated formulations comprising multiple enhancers (*e.g.*, bile salts in addition to a mixture of fatty acids) produced even better results (Example 7, page 53). Thus, Teng *et al.* teaches that a single fatty acid enhancer by itself is the least effective at enhancing delivery of nucleic acids. Teng *et al.* also shows that increasingly higher amounts of fatty acids provide improved results, ultimately using formulations comprising 8% fatty acids in combination with bile salts as preferred formulations (Examples 10 and up). Thus, Teng *et al.* provides no motivation to use a C10 fatty acid as the only enhancer to achieve effective absorption of nucleic acids.

Moreover, Teng *et al.* in Example 14 (page 65) demonstrates that decreasing the ratio of enhancer to nucleic acid in a formulation leads to decreases in bioavailability of the nucleic acid. In particular, Example 14 shows that a doubling of the amount of oligonucleotide relative to a constant amount of enhancer reduced the bioavailability of the oligonucleotide from about 18.0% to about 7.0% and a further doubling of the amount of oligonucleotide reduced the bioavailability to about 1.5%. Thus, Teng *et al.* teaches that substantially lowering the ratio of enhancer to nucleic acid in a formulation would be expected to have a negative effect on intracellular delivery of nucleic acids. This represents a true teaching away as it would lead one of ordinary skill in the art to believe that using concentrations within the claimed range would be ineffective. This is particularly true as the upper end of the claimed enhancer range (13 mM) is equal to 0.25% C10, or a 32-fold lower concentration of enhancer than the 8% enhancer present in the formulations of Example 14. As Example 14 demonstrates that lowering the ratio of enhancer to oligonucleotide 4-fold decreased bioavailability from about 18.0% to about 1.5%, one of ordinary skill in the art would expect

a 32-fold decrease in the amount of enhancer to result in negligible bioavailability of oligonucleotide. Furthermore, Example 14 show that the Examiner's statement that one of ordinary skill in the art would expect that the use of any amount of enhancer would still result in effective delivery is not supported by any evidence provided by the Examiner and contradicts the teaching of Teng *et al.*

The Examiner states that the lowest concentration of C10 used in the examples of Teng *et al.* is 0.5% in formulations 3, 15, and 17 which is less than 3 times the highest concentration of C10 enhancer encompassed by the claims. (Office Action, page 11). The Examiner further states that formulations 15 and 17 (which have 0.5% C10) show a higher absorption of nucleic acid (30.6% and 23.0%, respectively) than formulation 16 (1.0% C10, 19.7%), which does not support a contention that Teng *et al.* teaches away from using lower concentrations of a C10 enhancer. (Office Action, page 11).

Applicants respectfully disagree. The lowest concentration of C10 alone exemplified in Teng *et al.* is 1% (formulation 2). This is equivalent to a concentration of 51.5 mM, or about four times higher than the highest concentration recited in the present claims. All other examples of C10 in Teng *et al.* are in combination with other enhancers and thus outside the scope of the present claims. The Examiner's statement that formulations 15 and 17 comprising 0.5% C10 show a higher absorption than formulation 16 comprising 1.0% C10 is off base as each of the formulations comprise two other enhancers in addition to C10 that have a major influence on the absorption. In fact a close look at these formulations suggests that it is the amount of bile salt present that is most relevant to the level of absorption, with higher amounts resulting in more absorption. Thus, Teng *et al.* does not teach that lower amounts of C10 are better, and in fact teaches quite the opposite.

It is respectfully requested that the rejection of claims 1, 44–51, 55, and 56 under 35 U.S.C. § 103(a) be withdrawn.

(B) Claims 1 and 52 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Teng *et al.* in view of Lewin *et al.* (GB 23197673). (Office Action, page 2). Applicants respectfully traverse this rejection.

The Examiner alleges that Teng *et al.* is applied as above but does not teach that the nucleic acid based drug is a gene coding for an RNA molecule which functions in an

antisense capacity. (Office Action mailed December 24, 2009, page 5). The Examiner alleges that Lewin *et al.* teaches a nucleic acid vector which comprises a gene that expresses an RNA molecule which functions as an antisense oligonucleotide in a cell. The Examiner is of the opinion that it would have been *prima facie* obvious to modify the composition and method taught by Teng *et al.* to use the vector taught by Lewin *et al.* with a reasonable expectation of success, motivated by the knowledge of one of ordinary skill in the art that the vector could be used to produce large amounts of antisense RNA (Office Action mailed December 24, 2009, pages 5-6).

Applicants respectfully disagree. As described above, Teng *et al.* fails to teach or provide any incentive to use the concentration of enhancer as set forth in the present claims and in fact teaches away from the low concentrations claimed. Moreover, Teng *et al.* fails to teach or provide any incentive to use a C10 enhancer as the only enhancer in the composition. Lewin *et al.* fails to make up for the deficiencies of Teng *et al.* Lewin *et al.* describes a vector for expression of antisense RNA in cells (see Table 1). However, Lewin *et al.* is silent regarding the use of fatty acid enhancers. Lewin *et al.* does not provide any incentive to modify the teachings of Teng *et al.* by lowering the concentration of enhancer or using only a single enhancer. Thus, the present claims cannot be obvious over the cited combination of references.

It is respectfully requested that the rejection of claims 1 and 52 under 35 U.S.C. § 103(a) be withdrawn.

(C) Claims 57, 58, and 63-65 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Teng *et al.* in view of Akhtar (J. Drug Targeting 5:225 (1998)). (Office Action, page 2). Applicants respectfully traverse this rejection.

The Examiner alleges that Teng *et al.* is applied as above but does not teach that (1) the oligonucleotide is complexed with a cationic lipid or a polymer system; (2) an endosomal escape/nuclear accumulation agent can be used to facilitate delivery; (3) a condensing agent can be used to condense the oligonucleotide and facilitate delivery; and (4) a condensing agent can be used to condense the oligonucleotide and the oligonucleotide is complexed with a cationic lipid to facilitate delivery. (Office Action, page 4). The Examiner alleges that Akhtar teaches a number of different means for facilitating delivery of antisense

oligonucleotides into cells including the use of cationic lipids, polymer microspheres and agents to improve endosomal exit. (Office Action, page 4). The Examiner is of the opinion that it would have been *prima facie* obvious that delivery of the antisense oligonucleotide composition of Teng *et al.* could be facilitated using the means described in Akhtar with a reasonable expectation of success, motivated by the teaching of Akhtar that the means for facilitating delivery improves cellular delivery of antisense oligonucleotides. (Office Action, page 4). The Examiner further states that it would have been *prima facie* obvious to perform routine experimentation to determine the optimum and/or workable ranges of concentration for the C10 enhancer with a reasonable expectation of success. (Office Action, page 5).

Applicants respectfully disagree. As described above, Teng *et al.* fails to teach or provide any incentive to use the concentration of enhancer as set forth in the present claims and in fact teaches away from the low concentrations claimed. Moreover, Teng *et al.* fails to teach or provide any incentive to use a C10 enhancer as the only enhancer in the composition. Akhtar fails to make up for the deficiencies of Teng *et al.* Akhtar discusses the delivery of antisense oligonucleotides and mentions the use of different means for facilitating delivery (see Table 1). However, Akhtar is silent regarding the use of fatty acid enhancers. Akhtar does not provide any incentive to modify the teachings of Teng *et al.* by lowering the concentration of enhancer or using only a single enhancer. Thus, the present claims cannot be obvious over the cited combination of references.

It is respectfully requested that the rejection of claims 57, 58, and 63-65 under 35 U.S.C. § 103(a) be withdrawn.

(D) Claims 58-60 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Teng *et al.* in view of Akhtar (J. Drug Targeting 5:225 (1998)) and Akhtar *et al.* (Int. J. Pharmaceutics 151:57 (1997)). (Office Action, page 5). Applicants respectfully traverse this rejection.

The Examiner alleges that Teng *et al.* is applied as above but does not teach that (1) the oligonucleotide is complexed with a cationic lipid or a polymer system; (2) an endosomal escape/nuclear accumulation agent can be used to facilitate delivery; (3) a condensing agent can be used to condense the oligonucleotide and facilitate delivery; and (4) a condensing agent can be used to condense the oligonucleotide and the oligonucleotide is complexed with

a cationic lipid to facilitate delivery. (Office Action, page 6). The Examiner alleges that Akhtar teaches a number of different means for facilitating delivery of antisense oligonucleotides into cells including the use of polymer microspheres and that Akhtar *et al.* teaches that biodegradable polymers can be used to facilitate delivery of antisense oligonucleotides into cells, wherein the antisense oligonucleotide is complexed with (entrapped in) the polymer. (Office Action, pages 6-7). The Examiner is of the opinion that it would have been *prima facie* obvious that the antisense oligonucleotide composition of Teng *et al.* could be complexed with (entrapped in) a biodegradable polymer (such as PLGA) as taught by Akhtar *et al.* to facilitate the delivery of the oligonucleotide composition with a reasonable expectation of success, motivated by the teaching of Akhtar *et al.* that PLGA improves cellular delivery of antisense oligonucleotides. (Office Action, page 7). The Examiner further states that it would have been *prima facie* obvious to perform routine experimentation to determine the optimum and/or workable ranges of concentration for the C10 enhancer with a reasonable expectation of success. (Office Action, page 7).

Applicants respectfully disagree. As described above, Teng *et al.* fails to teach or provide any incentive to use the concentration of enhancer as set forth in the present claims and in fact teaches away from the low concentrations claimed. Moreover, Teng *et al.* fails to teach or provide any incentive to use a C10 enhancer as the only enhancer in the composition. Akhtar and Akhtar *et al.* both fail to make up for the deficiencies of Teng *et al.* Akhtar discusses the delivery of antisense oligonucleotides and mentions the use of polymer matrices (see page 231 and Table 1). However, Akhtar is silent regarding the use of fatty acid enhancers. Akhtar *et al.* discusses delivery of antisense oligonucleotides to cultured macrophages using biodegradable polymer (P(LA-GA)) particles (see abstract). However, Akhtar *et al.* is silent regarding the use of fatty acid enhancers. Neither reference provides any incentive to modify the teachings of Teng *et al.* by lowering the concentration of enhancer or using only a single enhancer. Thus, the present claims cannot be obvious over the cited combination of references.

It is respectfully requested that the rejection of claims 58-60 under 35 U.S.C. § 103(a) be withdrawn.

(E) Claims 61 and 62 have been rejected under 35 U.S.C. § 1 03(a) as allegedly being unpatentable over Teng *et al.* in view of Nakashima (J. Pharm. Sci. 84:1205 (1995)). (Office Action, page 8). Applicants respectfully traverse this rejection.

The Examiner alleges that Teng *et al.* is applied as above but does not teach that a P-glycoprotein inhibitor is administered with the antisense oligonucleotide composition. (Office Action, pages 8-9). The Examiner alleges that Nakashima *et al.* teaches that verapamil, a P-glycoprotein inhibitor, can be used in low doses in combination with antisense oligonucleotides to increase the efficacy of the antisense oligonucleotide treatment (Office Action, page 9). The Examiner is of the opinion that it would have been *prima facie* obvious to use verapamil in combination with antisense oligonucleotide compositions taught by Teng *et al.* with a reasonable expectation of success, motivated by the teaching of Nakashima *et al.* that low doses of the inhibitor increases the efficacy of the antisense oligonucleotide. (Office Action, page 9). The Examiner further states that it would have been *prima facie* obvious to perform routine experimentation to determine the optimum and/or workable ranges of concentration for the C10 enhancer with a reasonable expectation of success. (Office Action, page 9).

Applicants respectfully disagree. As described above, Teng *et al.* fails to teach or provide any incentive to use the concentration of enhancer as set forth in the present claims and in fact teaches away from the low concentrations claimed. Moreover, Teng *et al.* fails to teach or provide any incentive to use a C10 enhancer as the only enhancer in the composition. Nakashima *et al.* fails to make up for the deficiencies of Teng *et al.* Nakashima *et al.* discloses the use of an antisense oligonucleotide to the mdr1 mRNA (encoding P-glycoprotein) to reverse multidrug resistance in leukemia cell lines (abstract). Nakashima teaches that the addition of verapamil increased the reversal of resistance by the antisense oligonucleotide (page 1208, column 1, first full paragraph), due to verapamil's action as a strong inhibitor of P-glycoprotein (page 1206, column 2, last paragraph). Thus, verapamil is not associated in any way with enhanced delivery of the antisense oligonucleotide. Nakashima *et al.* is silent regarding the use of fatty acid enhancers. Thus, the present claims cannot be obvious over the cited combination of references.

It is respectfully requested that the rejection of claims 61 and 62 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

Applicants believe that the points and concerns raised by the Examiner in the Action have been addressed in full. It is respectfully submitted that this application is in condition for allowance, which action is earnestly solicited. Should the Examiner have any remaining concerns, it is respectfully requested that the Examiner contact the undersigned Attorney at (919) 854-1400 to expedite the prosecution of this application to allowance.

No fee is believed to be due with this response. However, the Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-0220.

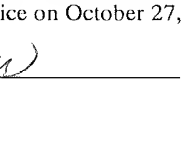
Respectfully submitted,

Robert A. Schwartzman, Ph.D.
Registration No. 50,211
Attorney for Applicants

USPTO Customer No. 20792
Myers Bigel Sibley & Sajovec
Post Office Box 37428
Raleigh, North Carolina 27627
Telephone: 919/854-1400
Facsimile: 919/854-1401

CERTIFICATION OF TRANSMISSION

I hereby certify that this correspondence is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4) to the U.S. Patent and Trademark Office on October 27, 2010.

Signature: 
Marthenn Salazar